CFSAN/Office of Nutritional Products, Labeling, and Dietary Supplements
September 8, 2004

Letter Responding to Health Claim Petition dated November 3, 2003 (Martek Petition): Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease

(Docket No. 2003Q-0401)

Mr. Martin J. Hahn

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Columbia Square

555 Thirteenth Street, NW

Washington, DC 20004-1109

RE: Health Claim Petition: Omega-3 Fatty Acids and Reduced Risk of Coronary Heart Disease (Docket No. 2003Q-0401)

Dear Mr. Hahn:

This letter responds to the qualified health claim petition dated November 3, 2003, submitted to the Food and Drug Administration (FDA or the agency), on behalf of Martek Biosciences Corporation (Martek petition) in accordance with the interim procedures for review of qualified health claims described in FDA's July 10, 2003 guidance for procedures on qualified health claims.[1] You submitted the petition as a comment to a petition from Jonathan W. Emord. Mr. Emord submitted the petition on behalf of Wellness Lifestyles, Inc. and Life Extension Foundation Buyers Club (collectively, the Wellness petition).

Your petition requested an extension of the existing omega-3 fatty acids and coronary heart disease (CHD) dietary supplement qualified health claim (a letter dated October 31, 2000,[2] a letter dated February 16,

2001,[3] a letter dated February 8, 2002[4]) to conventional foods including foods fortified with omega-3 fatty acids (specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)). Your petition proposed the model health claim: "A growing body of scientific literature suggests that higher intakes of the omega-3 fatty acids DHA and EPA may afford some degree of protection against coronary heart disease." For fish and shellfish, the petition proposed additional statements about potential risks of methylmercury. In your supplemental submission dated April 5, 2004, you requested modification of these statements.

FDA received the Wellness petition on June 23, 2003, for review under the standard health claim petition review process described in Section 403(r)(4) and 403 (r)(5)(D) of the Federal Food Drug and Cosmetic Act (the Act) (21 U.S.C. §§ 343(r)(4) and 343(r)(5)(D)). The Wellness petition requested that the agency authorize a health claim characterizing the relationship between omega-3 fatty acids (specifically EPA and DHA) and reduced risk of CHD. The Wellness petition requested that the disclaimer4 on the existing omega-3 fatty acids and CHD dietary supplement health claim be removed and that claim be extended to omega-3 containing foods. After corresponding with FDA, the petitioners elected to have their petition processed as a qualified health claim petition. FDA filed the Wellness petition on September 3, 2003 as a qualified health claim petition and posted the petition on the FDA website for a 60 day comment period, consistent with the interim procedures.

Because the substance and disease and the request for an extension of the existing omega-3 and CHD qualified health claim were the same in your petition and the Wellness petition, FDA consolidated the petitions in the same docket (Docket No. 2003Q-0401).

The agency received several comments on the petitions. You submitted two comments, one of which was a petition. Other comments were from industry, a professional organization, and an individual. The comments addressed various issues including the substance of the claim, mercury content in fish, safe upper limit of EPA and DHA, minimum effective levels of EPA and DHA, disqualifying nutrient levels, minimum nutrient content requirement, and claim statements. All support extending the omega-3 fatty acids and CHD qualified health claim to conventional foods. FDA considered the relevant comments in its evaluation of this petition.

This letter sets forth the basis of FDA's determination that the current evidence for the proposed health claim is appropriate for consideration for a qualified health claim on conventional foods and dietary supplements. This letter also sets out the factors that FDA intends to consider for the exercise of its enforcement discretion for a qualified health claim, for both conventional foods and dietary supplements, with respect to consumption of EPA and DHA omega-3 fatty acids and a reduced risk of coronary heart disease. This letter is an update to the previous letters on the use of a qualified health claim on EPA and DHA omega-3 fatty acid dietary supplements and coronary heart disease risk (the October 31, 2000 letter,[5] the February 16, 2001 letter,[6] and the February 8, 2002 letter[7]) and provides FDA's current thinking with respect to the use of this qualified health claim on both dietary supplements and conventional foods. Throughout the text of this letter, the phrase "omega-3 fatty acid qualified health claim" will be used to refer to the qualified health claim about the consumption of EPA and DHA omega-3 fatty acids and a reduced risk of coronary heart disease.

I. Overview of Data and Eligibility for a Qualified Health Claim

In a review of a qualified health claim, FDA considers the data and information provided in the petition, in addition to other data and information available to the agency that may assist in its review of the relationship between the substance and the disease or health-related condition. Consistent with its guidance entitled "Interim Evidence-based Ranking System for Scientific Data,"[8] the agency evaluates the scientific studies to determine what studies are pertinent to its review in evaluating the relationship. The agency may conclude that certain design flaws in a study are so significant that the study may not be helpful to the agency's decision about whether the particular study supports a relationship. Such design flaws may include the lack of a control group or the lack of any analysis of the data (Spilker et al., 1991; Federal Judicial Center, 2000).

In addition to human studies, FDA also considers other data and information in its review, such as meta-analyses,[9] review articles,[10] and animal[11] and *in vitro*[12] studies. These other types of data and information are useful in assisting the agency with an understanding of the scientific issues about a disease or health-related condition, but generally do not themselves establish a health claim relationship in the absence of supporting human intervention or observational data.

After the agency decides what scientific studies are relevant to its review about whether there is evidence to support a relationship between a substance and a disease or health-related condition, (i.e., what studies to rate based on study quality), the agency categorizes these studies into: (1) the most persuasive studies, which are studies designed to evaluate whether there is a relationship between the substance and disease outcome (e.g., intervention studies that manipulate the intake level of the substance while controlling for other factors that can affect disease risk reduction and/or; (2) less persuasive studies (e.g., studies that my have design flaws that make them less reliable in evaluating a substance/disease relationship or less applicable to the U.S. population (conducted in countries where usual intakes of the substance is much lower or higher than in the U.S.). The most persuasive studies are given the greatest consideration. FDA rates the most and less persuasive studies for quality. Scientific quality is based on several criteria including study population, intervention design (e.g., presence of a placebo control), data collection (e.g., dietary assessment method), statistical analysis, and outcome measures. For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high quality rating. Lower quality ratings (e.g., moderate and low) would be given based on the extent of the deficiencies or uncertainties in the quality criteria.

Collectively, FDA then rates the strength of the total body of evidence that it determines is relevant to its review, using criteria such as the study type (e.g., intervention), quality, quantity (number of the various types of studies and sample sizes), and consistency of the results. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support the substance/disease relationship, and if so, then determines the ranking that reflects the level of comfort among qualified scientists that such a relationship is scientifically valid.

The Martek petition cited 42 publications as evidence to substantiate the relationship for this claim. These publications consisted 6 intervention studies on EPA and DHA omega-3 fatty acids and CHD,[13] 7 observational studies on EPA and DHA omega-3 fatty acids and CHD,[14] 5 studies on alpha linoleic acid (ALA) and CHD,[15] 13 review articles,[16] 2 meta-analyses,[17] 1 position paper,[18] 4 editorial comments,[19] 2 chapters from the IOM Report,[20] 2 studies on the safety of fish and fish oils,[21] and 1 abstract.[22]

The agency did not consider all the publications cited in the Martek petition to be pertinent to its review of this substance/disease relationship. While useful for background information, the review articles, position paper, editorial comments, meta-analyses and abstract did not contain sufficient information on the individual studies reviewed and therefore FDA could not determine their pertinence regarding factors such as the study population characteristics or the composition of the products used (e.g., food, dietary supplement); similarly, the lack of detailed information on the studies summarized in the review articles, position paper, editorial comments, meta-analyses and abstract did not allow FDA to determine if the studies are flawed in critical elements such as its design, execution, and data analysis. FDA must review the scientific quality of a study to determine whether credible conclusions can be drawn from it.

In addition to the studies in your petition that the agency considered, FDA considered an additional 7 intervention studies (5 from the Wellness petition[23]; 1 from a comment [24]; 1 identified by FDA through a literature search[25]), and 4 observational studies from the Wellness petition.[26]

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petitions identified the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as the substance for the proposed claim. EPA and DHA are components of some fatty fish

(primarily cold water fish),[27] fish oils, other foods (e.g., seaweed), dietary supplements, and food ingredients (e.g., algal oils). Therefore, the agency concludes that the substances, EPA and DHA omega-3 fatty acids, identified in the petition are components of food and therefore meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified coronary heart disease (CHD) as the disease for the proposed claim. The agency concludes that CHD is a disease and therefore that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5).

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim must be demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act.

The Wellness petition stated that omega-3 fatty acids, as EPA and DHA, have been a naturally occurring ingredient in foods consumed safely in the United States prior to January 1, 1958, and that there is no evidence that when consumed either in foods or as dietary supplements there is a cumulative effect in the diet that is unsafe. The Martek petition stated that omega-3 fatty acids occur in conventional foods with a long history of safe use, such as fish, and are generally recognized as safe (GRAS) when used as direct food ingredients intended to increase omega-3 fatty acids. Some comments to the petition expressed an interest in using the omega-3 fatty acid qualified health claim for foods that contain EPA and DHA as a food ingredient from sources including fish oil and algal oil.

In order to meet the safe and lawful requirement for health claims (21 CFR 101.14(b)(3)(ii)), the use of EPA and DHA omega-3 fatty acid, when used in conventional food or as a dietary supplement at levels necessary to justify the claim, must be demonstrated, to FDA's satisfaction, to be safe and lawful. FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is GRAS, approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)). Dietary ingredients in dietary supplements, however, are not subject to the food additive provisions of the act (see section 201(s)(6) of the Act (21 U.S.C. § 321(s)(6)). Rather, they are subject to the adulteration provisions in section 402 of the Act (21 U.S.C. 342) and, if applicable, the new dietary ingredient provisions in section 413 of the Act (21 U.S.C. 350b), which pertain to dietary ingredients that were not marketed in the United States before October 15, 1994. The term "dietary ingredient" is defined in section 201(ff)(1) of the act and includes vitamins; minerals; herbs and other botanicals; dietary substances for use by man to supplement the diet by increasing the total daily intake; and concentrates, metabolites, constituents, extracts, and combinations of the preceding types of ingredients.

In 1997, FDA affirmed, as GRAS, menhaden oil as a direct human food ingredient with specific limitations of use to ensure that the total daily intake of EPA and DHA would not exceed 3.0 grams per person per day (g/p/d) (62 FR 30751; June 5, 1997; 21 CFR184.1472). EPA and DHA are the major omega-3 fatty acids in fish oil and together comprise about 20 percent by weight of menhaden oil. FDA established maximum use levels of menhaden oil in certain foods because of concerns over possible adverse effects of fish oil consumption on bleeding time, glycemic control, and LDL cholesterol (62 FR 30751 at 30757; June 5, 1997). In 2002, FDA published a proposed rule to reallocate the uses of menhaden oil in conventional food, while maintaining the total daily intake of EPA and DHA from menhaden oil at a level not exceeding 3.0 g/p/d (67 FR 8744; February 26, 2002). FDA placed specific limitations, including the category of foods, the functional use of the ingredient, and the level of use, to ensure that the consumption of EPA and DHA from

conventional food sources would not exceed 3.0 g/p/d. FDA then published a tentative final rule (69 FR 2313; January 15, 2004) to additionally require that menhaden oil not be used as an ingredient in foods in combination with other added oil that is a significant source of EPA and DHA to ensure that total intake from conventional food sources do not exceed 3.0 g/p/d.

In addition, FDA has not objected to certain GRAS notifications for additional sources of EPA and DHA as food ingredients (fish oils other than menhaden oil) (GRAS Notice Nos: GRN000097, GRN000102, GRN000105, GRN000109, GRN 000137, GRN000138).[28] These GRAS notices proposed maximum use levels consistent with those specified in the tentative final rule affirming, as GRAS, menhaden oil as a direct human food ingredient with specific limitations of use.

FDA has also responded without objection to a GRAS notification on algal oil DHA from Martek Biosciences Corporation. Martek estimated that the use of algal oil in a number of food categories at the maximum proposed use levels would result in a mean exposure of no more than 1.5 grams of DHA per day (GRAS Notice No. GRN000137).

The mean exposure to EPA and DHA from menhaden oil in all conventional food categories is estimated to be 2.7 g/p/d (67 FR 8744 at 8746; February 26, 2002). This is a conservative estimate with substantial margin for safety, and the agency believes, consistent with its prior decision on the use of a qualified health claim for DHA and EPA omega-3 fatty acids (October 31, 2000 letter), that the addition of menhaden oil to food products has not come close to this conservative mean estimate exposure. FDA further believes that the GRAS uses for which it received a GRAS notification for other sources of EPA and DHA omega-3 fatty acids also provide conservative estimates of exposure and that the addition of these EPA and DHA sources to food products do not come close to the conservative mean estimates. Not all foods in the marketplace within those permitted food categories would contain menhaden oil or other sources of EPA and DHA omega-3 fatty acids that substitute for other edible fat or oil. Also, because not all foods that a consumer eats every day would contain menhaden or other EPA and DHA oil used as a substitute oil, the actual total daily intakes of EPA and DHA from menhaden or other EPA and DHA oil for an average person should be significantly below 3.0 g/p/d (67 FR 8744 at 8746; February 26, 2002).

It is difficult to estimate the actual total consumption of EPA and DHA. The Continuing Survey of Food Intakes by Individuals (1994-1996, 1998)[29] estimated EPA and DHA intakes from conventional foods.[30] The 50th percentile intake of EPA and DHA from the survey was between 0.06 g and 0.07 g for adult women and 0.07 g and 0.1 g for adult men. The 90th percentile intake was between 0.18 g and 0.22 g for women and between 0.20 g and 0.43 g for men. Thus, EPA and DHA consumption from conventional foods in the United States is low. FDA is not aware of any nationally representative consumption data on EPA and DHA from dietary supplements. In the October 31, 2000 letter, FDA expressed concern about the exposure to EPA and DHA omega-3 fatty acids potentially exceeding 3.0 g/p/d if a qualified health claim were to appear on dietary supplements. This concern was due to conventional foods containing omega-3 fatty acids that were on the market; the use of structure/function claims on products containing EPA and DHA omega-3 fatty acids, which may promote product purchase; and dietary supplements that FDA found in the marketplace that contained significant amounts of EPA and DHA.

With this letter, the requested use of this qualified health claim is now extended to conventional foods. The agency believes that there is likely to be some increased consumption of EPA and

DHA omega-3 fatty acids based on conventional foods that bear the qualified health claim; however, the amounts of EPA and DHA that can be used and the foods in which such food ingredients can be safely used are limited. The agency has established specific limitations of use under its menhaden oil GRAS rule (62 FR 30751; June 5, 1997), proposed and tentatively finalized reallocation of the use of menhaden oil without changing total exposure levels (67 FR 8744; February 26, 2002, 69 FR 2313; January 15, 2004). Also, manufacturers that have submitted GRAS notifications for other sources, to which the agency has not objected, have established conditions of use similar to those in the menhaden oil GRAS rule.

In the October 31, 2000 letter,[31] FDA stated that a consumer could consume nearly 1 gram of EPA and DHA per day in the diet from conventional foods. The agency is uncertain about how much consumers will increase their intake of EPA and DHA omega-3 fatty acids from EPA and DHA containing conventional foods and dietary supplements due to the extended use of the qualified health claim. In order to help consumers gauge their total intake of EPA and DHA and to provide them a way to keep their intake of EPA and DHA within 3 grams per day, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods and dietary supplements that bear an omega-3 fatty acid qualified health claim declare the amount of EPA and DHA per serving in the claim. FDA recommends that the information on EPA and DHA content for use in a qualified health claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD be presented in a manner that is consistent with FDA's guidance entitled, "FDA Nutrition Labeling Manual--A Guide for Developing and Using Data Bases." You may contact CFSAN's Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS) for further information. The dietary supplement may declare the amount of EPA and DHA per serving in "Supplement Facts," instead of making the declaration in the claim. Also, to ensure further that consumers do not exceed a 3.0 g/p/d intake, FDA will educate consumers not to exceed 3.0 g/p/d from all food and dietary supplement sources through print and web outreach information. Further, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements not recommend or suggest in labeling that consumers ingest more than 2 grams of EPA and DHA per day. FDA encourages manufacturers to limit their dietary supplement products bearing the qualified health claim to products recommending or suggesting daily intake of 1 gram or less of EPA and DHA omega-3 fatty acids.

Based on the data and information that FDA considered, which includes data and information that FDA relied upon in reaching its conclusions about the safety of EPA and DHA omega-3 fatty acids in its GRAS affirmation of menhaden oil, the data and information in the 1991 proposed (56 FR 60663; November 27, 1991) and 1993 final rules (58 FR 2683; January 6, 1993), and its current scientific literature review for other possible safety concerns, FDA concludes that the use of EPA and DHA omega-3 fatty acids used as a GRAS ingredient, consistent with FDA's GRAS rule for menhaden oil and GRAS notifications to which FDA did not object, and the use as a dietary supplement is safe and lawful under 21 CFR 101.14 provided that daily intakes of EPA and DHA omega-3 fatty acids from conventional food and dietary supplement sources do not exceed 3.0 g/p/d. In section IV, FDA sets forth factors under which it plans to exercise enforcement discretion for EPA and DHA containing conventional foods and dietary supplements bearing the qualified claim, to ensure, among other things, that such use will be safe.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified the following endpoints to use in identifying CHD risk reduction for purposes of a health claim evaluation for EPA and DHA omega-3 fatty acids: Coronary events (MI, ischemia), cardiovascular death, atherosclerosis, and high blood pressure. Artherosclerosis is the underlying cause of CHD, which can lead to the signs of CHD including coronary events (MI, ischemia) and cardiovascular death.[32] High blood pressure, serum total cholesterol, serum LDL-cholesterol, and serum HDL-cholesterol are considered as surrogate endpoints for CHD.[33] However, FDA concluded in its October 31, 2000 letter[34] that omega-3 fatty acids do not affect serum cholesterol levels (total, LDL, HDL). To evaluate the potential effects of EPA and DHA omega-3 fatty acid consumption on CHD risk, FDA considered coronary events (myocardial infarction (MI), ischemia), cardiovascular death, atherosclerosis, and high blood pressure as indicators or predictors of disease.

In considering the qualified health claim for EPA and DHA omega-3 fatty acid dietary supplements in October 2000, FDA focused on human data that had become available since FDA's 1991-93 review and on human studies that quantitatively measured or estimated the omega-3 fatty acid intakes in relation to a direct measure of CHD risk or a surrogate endpoint for CHD risk. Several, but not all, of the studies[35] that FDA had considered in its October 31, 2000 letter were submitted in the Wellness petition. Studies that have been published since that letter were also included in the petitions. For purposes of this review, FDA, in

determining the scientific support for a relationship between EPA and DHA omega-3 fatty acid dietary supplements and CHD, focused on the more recent studies to determine whether these studies added any support to the scientific evidence that was used for the current qualified health claim for EPA and DHA omega-3 fatty acid dietary supplements. For purposes of determining whether there is a relationship between EPA and DHA omega-3 fatty acids from conventional foods and reduced risk of CHD, FDA determined whether the relevant studies cited in the petition, in addition to other relevant studies that the agency had already reviewed in its previous reviews support a qualified health claim.

A. Assessment of the Intervention Studies

FDA identified a total of 10 intervention studies, not previously reviewed in 2000, for its current review of this qualified health claim (6 from the current petition[36]; 2 from the Wellness petition[37]; 1 from a comment[38]; 1 identified by FDA through a literature search[39]). FDA did not consider some of these studies in its current review for the following reasons: 1) Marchioli, et al. (2002) was a reanalysis of GISSI et al. (1999), which FDA reviewed in 2000, and provided no additional evidence relevant for establishing a substance-disease relationship; 2) Thies et al. (2003) and Maresta et al. (2002) measured outcomes (plaque stability and percutaneous transluminal coronary angioplasty (PTCA), respectively) that are not recognized as valid surrogate endpoints for CHD; 3) the studies by Ghafoorunissa et al. (2002), Laidlaw and Holub, et al. (2003) did not include control groups for EPA and DHA (Spilker, 1991); 4) Leng et al. (1998) did not include a control for gamma-linolenic acid (GLA), which constituted the majority of the treatment (approximately six times higher than EPA), thus there is no way to determine whether the effects were due to EPA; and 5) two intervention studies that reported no benefit on CHD incidence (Angerer et al., 2002; Nilsen et al., 2001) were conducted in CHD patients and the results could not be extrapolated to the general healthy population; therefore, these data were not considered relevant to FDA's review for establishing a substance-disease relationship in the general population. Thus, FDA considered only 2 intervention studies identified since the 2000 review as capable of supporting the substance/disease relationship (Finnegan et al., 2003; Woodman et al., 2002).

The studies by Finnegan et al. (2003) and Woodman et al. (2002) were randomized, placebo-controlled, double-blind[40] intervention studies that reported the effects of fish oil on blood pressure. Finnegan et al. (2003) reported the results from a study involving 150 moderately hyperlipidemic subjects[41] assigned to 1 of 5 interventions: fish oil (0.8 or 1.7 g/day EPA+DHA); rapeseed and linseed oil (4.5 or 9.5 g/day ALA), or an n-6 PUFA control (sunflower and safflower oil) for 6 months. The fish oil intervention provided no benefit in CHD risk factors, including blood pressure, compared to the placebo control group. Woodman et al. (2002) was a 6-week intervention comparing EPA ethyl ester[42] (4 g/day) or DHA ethyl ester42 (4 g/day) with olive oil (4 g/day) in type 2 diabetics[43] with hypertension (n=52). Neither EPA ethyl ester nor DHA ethyl ester provided any benefit to blood pressure or any other CHD risk factor compared with the olive oil treated patients.

B. Assessment of the Observational Studies

FDA identified 10 observational studies not previously reviewed in 2000. These consisted of 6 prospective cohort studies (4 from the current petition[44]; 2 from the Wellness petition[45]), 3 nested case-control studies (2 from the current petition[46]; 1 from the Wellness petition[47]), and 1 ecological study from the current petition.[48]

Two of the 10 studies on fish consumption and CHD[49] were not considered in this review because these studies only reported total fish consumption without providing details of the fish type[50] or portion sizes, thus there is no way of knowing how much, if any, EPA and DHA omega-3 fatty acid was consumed. The remaining 8 observational studies[51] were of high to moderate quality. These observational studies provide only an estimated intake of EPA and DHA omega-3 fatty acids from fish consumption and provided only an association with disease risk, and not direct causality of disease risk.

Hu et al. (2002) reported results from the Nurses' Health Study, a prospective cohort study on female registered nurses (n=84,688) with a 16 year follow-up. Fish and omega-3 fatty acid intake were calculated as an average intake from all available dietary questionnaires up to the start of each 2-year follow-up interval in which events were reported. There was an inverse correlation observed between fish/omega-3 fatty acid consumption and incidence of CHD, including CHD deaths and nonfatal MI. A subgroup analysis of diabetic nurses from this cohort (n=5,103; Hu et al., 2003) observed a reduced risk of CHD from fish consumption but the association did not extend to estimated EPA and DHA omega-3 fatty acid consumption.

Albert et al. (2002) was a case-control study nested in the U.S. Physicians Health Study (Albert et al., 1998), which was considered in the 2000 review. The nested case-control study had a 17-year follow-up and reported a significant inverse relationship between whole blood omega-3 fatty acid concentrations and CHD death.

The study by Rissanen et al. (2000) reported 10-year follow-up results from the Kuopio Ischemic Heart Disease Risk Factor Study, which is an ongoing, prospective, population-based cohort study investigating risk factors for cardiovascular disease (CVD) and is part of the World Health Organization's (WHOs) MONICA project. The study enrolled 1,871 men who had no clinical CHD at baseline examination. The authors reported a decrease in acute coronary events in men at the highest quintile[52] of serum DHA+DPA[53] concentration compared with men at the lowest quintile.

Results from the Cardiovascular Health Study were reported by Mozaffarian et al. (2003). In this prospective cohort study, men (~1,500) and women (~2,400) aged ≥65 years were enrolled who were free of known CVD at baseline in 1989-1990 and had data on fish consumption. During the 9.3 years of follow-up, there were 247 ischemic heart disease (IHD)[54] deaths and 363 MIs. Estimated intake of EPA + DHA at baseline (0.55 g/day and 0.92 g/day) was associated with lower risk of fatal ischemic heart disease (IHD), but there was no association between EPA + DHA and non-fatal MI. This result is consistent with the report from a case-control study nested in the Cardiovascular Health Study (Lamaitre et al., 2003). A higher plasma concentration of EPA + DHA was associated with a lower risk of fatal IHD, but there was no association between plasma concentration of EPA + DHA and a risk of non-fatal IHD.

Hallgren et al. (2001) was a case-control study nested in the Västerbotten Intervention Programme, which was part of the WHOs MONICA project. In this study, 78 people (cases) developed an MI, and were matched against 156 controls subjects that were randomly selected from the study. Fish intake was assessed by a food frequency questionnaire (FFQ).[55] In addition, fatty acid composition of the plasma phospholipids, including EPA and DHA, was analyzed. There was no correlation between fish intake or blood EPA+DHA and acute MI.

Torres et al. (2000) compared fish consumption in Portuguese men living in a fishing village (n=50) or rural village (n=37) with IHD-related deaths based on death certificate records for the population. There was significantly more fish consumed in the fishing village compared with the rural village and this correlated with lower IHD deaths estimated from death certificate records for the two villages.

C. Other Data and Information

The Institute of Medicine (IOM) of the National Academy of Sciences has stated in its most recent Macronutrient Report that "Growing evidence suggests that dietary *n-3* polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reduce the risk of coronary heart disease (CHD) and stroke."[56] Therefore, by concluding that there was only "growing evidence" that is "suggestive" of the relationship for this proposed claim, the IOM recognized limitations in the current data on omega-3 and its ability to reduce risk of CHD.

III. Strength of the Scientific Evidence

FDA relies primarily on human studies that are primary reports of data collection when attempting to establish a diet-disease relationship and has consistently identified two endpoints with which to identify

disease risk reduction for purposes of health claims evaluations: a) reduction in incidence of the disease, and; b) beneficial changes in surrogate endpoints for the disease.[57] The most persuasive evidence for a relationship between EPA and DHA omega-3 fatty acids and reduced risk of CHD would be from intervention studies with EPA and DHA omega-3 fatty acids demonstrating reduced incidence of CHD in healthy populations (i.e., primary prevention). However, no such studies for EPA and DHA omega-3 fatty acids and CHD were identified. There were 2 small intervention studies in healthy populations that measured EPA and DHA effects on blood pressure, a CHD surrogate endpoint, but no benefit was observed in these studies. Thus, the scientific evidence from intervention studies available since the 2000 review with EPA and DHA omega-3 fatty acids as the test substance, did not show a relationship between omega-3 fatty acids and reduced risk of CHD in the general population.

The remaining studies considered were high to moderate quality observational studies on healthy populations. Of these, 3 studies (Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003 (also Lamaitre et al., 2003)) were conducted in populations relevant to the general U.S. population, across a broad age range (30 to 84 years) and consistently reported that EPA and DHA omega-3 fatty acids reduced the risk of CHD. The largest cohorts followed 84,688 women (Hu et al., 2002) and 20,551 men (Albert et al., 1998, 2002). Of the observational studies conducted in populations considered less relevant to the general U.S. population, 1 small study (n=78 cases) (Hallgren et al. 2001) reported no benefit; whereas 2 studies (Rissanan et al, 2000; Torres et al., 2000) with sample sizes of 1,871 and 50, respectively, reported an associated benefit. Observational studies provide less compelling evidence than intervention studies for a relationship between omega-3 fatty acids and reduced risk of CHD because they provide only an estimated intake of EPA and DHA omega-3 fatty acids rather than a direct measure. In addition, observational studies cannot separate the effect of EPA and DHA omega-3 fatty acids from the effects of other food components, and therefore it is not clear whether any purported benefit is related to the EPA and DHA omega-3 fatty acids or to other dietary factors. Observational studies provide only supportive rather than direct evidence for a relationship. For these reasons, FDA considers observational studies as less persuasive than intervention studies conducted in a general healthy population for establishing a substance-disease relationship. Nevertheless, primary prevention of CHD in healthy populations by EPA and DHA omega-3 fatty acids was observed in the majority of observational studies reviewed, which included 2 large prospective cohorts conducted in the US, the Nurses' Health Study (n=84,688; 16 year follow-up; Hu et al., 2002) and the U.S. Physicians Health Study (n=20,551; 11 to 17 year follow-up; Albert et al., 1998, 2002). In sum, the majority of observational studies consistently observed an associated CHD risk reduction from intake of EPA and DHA estimated from the diet in men and women in populations relevant (3 studies) or less relevant (2 studies) to the general U.S. population.

Given the inability of predicting CHD risk reduction in a general healthy population based on secondary prevention studies in diseased populations, and the limitations of the observational studies in separating the effects of EPA and DHA omega-3 fatty acids from other dietary factors, the agency evaluated other available evidence, as discussed in the October 31, 2000 letter, that provide support for a qualified health claim for EPA and DHA omega-3 fatty acids and reduced risk of CHD. As described in detail in the October 31,2000 letter,[58] FDA considered: (1) observational studies in the general healthy population in which fish consumption was the primary contributor of EPA and DHA omega-3 fatty acids, and (2) intervention studies in both the general healthy population and patients with established CHD that evaluated the effects of EPA and DHA omega-3 fatty acids on physiological endpoints (e.g., total cholesterol, LDL-cholesterol, HDL-cholesterol, VLDL-cholesterol, triglycerides, platelet aggregation), some of which have been proposed as possible mechanisms for the CHD risk reduction by EPA and DHA omega-3 fatty acids. Thus, FDA is not changing its position from that outlined in the October 31, 2000 letter on the EPA and DHA omega-3 fatty acid and CHD qualified claim that there is sufficient suggestive evidence that the benefit on CHD reported in CHD patients (i.e., secondary prevention) (reviewed in the October 31, 2000 letter) applies to the general population because of: (1) The primary CHD prevention in the general population associated with EPA and DHA consumption from fish in observational studies; and, (2) intervention studies demonstrating similar physiological effects of EPA and DHA in both the diseased and general populations. FDA still concludes

that the weight of the scientific evidence for a health claim for EPA and DHA omega-3 fatty acids outweighs the scientific evidence against such a claim. The most significant change in the available body of evidence since 2000 is the additional observational studies, the majority of which consistently reported an associated benefit in CHD risk from EPA and DHA consumption from fish.

The observational studies estimating EPA and DHA omega-3 fatty acid intake from conventional foods support the expansion of the existing qualified health claim for EPA and DHA omega-3 fatty acids from dietary supplements and CHD to conventional foods. Therefore, FDA intends to consider the exercise of its enforcement discretion with regard to a qualified health claim on the label or in labeling of EPA and DHA omega-3 fatty acid-containing dietary supplements and conventional foods that provides a truthful and non-misleading description of the strength of the body of scientific evidence, e.g., "supportive but not conclusive research shows." Other factors that FDA intends to consider in deciding whether to exercise its enforcement discretion with regard to the use of this qualified health claim on particular foods, including dietary supplements, are discussed below.

IV. Other Enforcement Discretion Factors

Factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims about EPA and DHA omega-3 fatty acids and reduced risk of coronary heart disease are discussed below. You should also know that FDA is considering its enforcement discretion as applying only to such foods in which EPA and DHA is an added ingredient that FDA has approved as a food additive or affirmed as GRAS or for which the agency has received a GRAS notification to which it did not object.

A. Total fat, Saturated Fat, and Cholesterol Criteria for CHD-related Health Claims

In regulations authorizing CHD-related health claims, FDA has generally required, with a few exceptions, that foods bearing such claims meet the "low fat" criterion defined by 21 CFR 101.62(b)(2), the "low saturated fat" criterion defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR sections 101.75, 101.77, 101.81, 101.82, and 101.83). The agency discusses below how the agency intends to consider these criteria as factors in deciding whether to exercise its enforcement discretion for an omega-3 fatty acid qualified health claim on conventional foods and dietary supplements. Later in Section B, FDA discusses total fat, saturated fat, and cholesterol content disqualifying levels relative to the general requirement for health claims (21 CFR 101.14(a)(4)).

"Low fat" criterion

FDA has required in the past that foods bearing CHD health claims meet the requirement for "low fat" as defined by 21 CFR 101.62(b)(2). The requirement of the "low fat" criterion was first introduced in the dietary lipid and cardiovascular disease proposed rule (56 FR 60727 at 60739; November 27, 1991). FDA stated that, although total fat is not directly related to increased risk for CHD, it may have significant indirect effects. The agency stated that low fat diets facilitate reduction in the intake of saturated fat and cholesterol to recommended levels. Furthermore, the agency noted that obesity is a major risk factor for CHD, and dietary fats, which have more than twice as many calories per gram as proteins and carbohydrates, are major contributors to total calorie intakes. There have been several exceptions to this criterion in the past. Instead of the "low fat" criterion, fish and game meat are required to meet the "extra lean" criterion in the saturated fat and cholesterol and CHD health claim (21 CFR 101.75(c)(2)(ii)). Products derived from whole soybeans without added fat are exempted from the "low fat" criterion in the soy protein and CHD health claim (21 CFR 101.82(c)(2)(iii)(C)). In the plant sterol/stanol esters and CHD health claim, FDA does not require the "low fat" criterion but requires that total fat level of foods not exceed the total fat disqualifying level (21 CFR 101.14(a)(4)) with an exception for spread and dressing for salad on a per 50 g basis (21 CFR 101.83(c)(2)(iii)(C)). In not requiring the "low fat" criterion, FDA noted that the Dietary

Guidelines for Americans, 2000 (USDA & DHHS, 2000) recommended choosing a diet that is low in saturated fat and cholesterol and moderate in total fat. Specifically, the Dietary Guidelines recommended moderate amounts of foods high in unsaturated fat with a caution to avoid excess calories.

FDA concurs with the dietary guidelines that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk, than consuming diets low in total fat. Therefore, FDA has decided not to consider, as a factor in the exercise of its enforcement discretion, that either dietary supplements or conventional foods that bear an omega-3 fatty acid qualified health claim meet the "low fat" criterion.

"Low saturated fat" and "low cholesterol" criteria

In regulations authorizing CHD health claims, FDA has also generally required that foods bearing the claims meet the "low saturated fat" criterion as defined by 21 CFR 101.62(c)(2), and the "low cholesterol" criterion as defined by 21 CFR 101.62(d)(2) (see authorized claims in 21 CFR sections 101.75, 101.77, 101.81, 101.82, and 101.83). FDA continues to believe that these criteria are important. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that conventional foods or dietary supplements that bear an omega-3 fatty acid qualified health claim meet the "low saturated fat" and "low cholesterol" criteria. However, there are some situations, as discussed below, when FDA does not believe that such a factor is important to a decision about the exercise of its enforcement discretion.

Low saturated fat

FDA intends to consider, as a factor in the exercise of its enforcement discretion, that individual foods other than fish that bear an omega-3 fatty acid qualified health claim, meet the "low saturated fat" criterion (21 CFR 101.62(c)(2)). This food category includes primarily foods enriched with EPA- and DHA-containing food ingredients. FDA intends to consider, as a factor in the exercise of its enforcement discretion for meal products as defined in 21 CFR 101.13(l) and main dishes as defined in 21 CFR 101.13(m) that such foods meet all criteria specified for the "low saturated fat" criteria (21 CFR 101.62(c)(2)). FDA believes that many foods would meet the "low saturated fat" criteria, as stated in the final rule for nutrient content claims (58 FR 2302 at 2339; January 6, 1993). The criteria, "no more than 15 percent of calories from saturated fat" for individual foods can be achieved due to calorie contribution from food ingredients other than fish oil in these foods. Later in this section, FDA defines fish as "products that are essentially all fish" and identifies nutrient content factors that it intends to consider in the exercise of its enforcement discretion for the qualified health claim.

FDA intends to exercise its enforcement discretion for EPA- and DHA-containing dietary supplements (whether softgels or liquid forms) that bear an omega-3 fatty acid qualified health claim, and that meet the low saturated fat criterion per reference amount customarily consumed (RACC). However, FDA does not intend to consider, as a factor in the exercise of its enforcement discretion, that "no more than 15 percent of calories be from saturated fat." In a fish oil, 20 - 30 percent of calories come from saturated fat (USDA National Nutrient Database for Standard Reference, Release 17). Because 100 percent fish oil dietary supplements usually have no other source of calories other than fish oil and reformulation is not possible to reduce percent of calories from saturated fat, fish oil dietary supplements would not be eligible for the qualified health claim if FDA decided to consider the 15 percent criterion in 21 CFR 101.62(c)(2) as a factor in the exercise of its enforcement discretion. FDA believes that not considering the 15 percent criterion as a factor in the exercise of its enforcement discretion is appropriate given that fish oils are derived from fish, which have been shown to be associated with a reduced risk of CHD in observational studies with healthy individuals. In the algal oil used in Martek's dietary supplements, 40 - 45 percent of the oil is DHA and 30 - 40 percent of calories come from saturated fat.[59] Because the algal oil is diluted by high oleic sunflower oil by 7 - 10 percent or by 50 - 60 percent to make the final DHA concentration specific to Martek's products (either 20 percent or 40 percent DHA), calorie contribution from saturated fat will be either a little less than 30 - 40 percent (for the 40 percent DHA product) or about 15 - 20 percent of calories (for the 20 percent DHA product). In the final oil, calories from saturated fat exceed 15 percent; however, the level overlaps with that of fish oils. Therefore, FDA intends to consider, as a factor in the exercise of its enforcement discretion, that dietary supplements that bear an omega-3 fatty acid qualified health claim meet the "equal to or less than 1 g of saturated fat per RACC" criterion in 21 CFR 101.62(c)(2) but does not intend to consider

the "no more than 15 percent of calories from saturated fat" criterion as a factor in the exercise of its enforcement discretion.

Low cholesterol

FDA intends to exercise enforcement discretion for an omega-3 fatty acid qualified health claim for individual foods, other than fish and dietary supplements, provided that such foods meet the low cholesterol criteria (21 CFR 101.62(d)(2)). The October 31, 2000 letter[60] and subsequent letters from FDA[61], [62] did not discuss the low cholesterol criteria for dietary supplements; however, most fish oil containing dietary supplements do not meet the low cholesterol criteria per 50 g. Most dietary supplements containing EPA and DHA omega-3 fatty acids (whether fish oils or algal oils) are in softgels, and the amount of these oils per RACC is very small. Serving sizes are usually in between 1 - 2 softgels. FDA estimates that 1 - 2 softgels may weigh about 1 - 3 g, containing about 0.5 - 2 g of fish oil or algal oil. This amount of fish oil would not exceed the "low cholesterol" criteria (20 mg) per RACC but would exceed the "low cholesterol" criteria per 50 g basis if the supplements contain 100 percent fish oil. Liquid forms of fish oil dietary supplements are much less common and provide usually one teaspoon as a serving size (containing 4.5 g of total fat). This amount of fish oil may contain about 22 - 34 mg of cholesterol (based upon USDA National Nutrient Database for Standard Reference, Release 17), but again such levels of consumption would not be common.

Algal oil dietary supplements are sold as softgels and the RACC of the supplement is one softgel, containing 0.5 g of the mixture of algal oil and high oleic sunflower oil.[63] Both the 100 mg DHA softgel and the 200 mg DHA softgel contain less than 2 mg of cholesterol, which is below the "low cholesterol" criteria (20 mg) per RACC. The cholesterol content of algal oil will vary. The algal oil that Martek proposed to use for various food categories in its GRAS notification (GRAS No. 000137) contains higher levels of cholesterol (about 380 mg/100g without dilution) than does the algal oil currently used for dietary supplements (about 30 mg/100g without dilution). Even if the algal oil with the high cholesterol content were used for dietary supplements, the cholesterol content per RACC would be very small (about 2 mg of cholesterol) because the amount of oil per serving (0.5 g) is small, but the cholesterol content would exceed the "low cholesterol" criteria (20 mg) per 50 g basis.

FDA estimates that 50 g of fish oils would contain about 240 to 380 mg of cholesterol (USDA National Nutrient Database for Standard Reference, Release 17). The algal oil currently used for dietary supplements (without the addition of sunflower oil) contains about 15 mg of cholesterol per 50 g.[64] The algal oil that Martek proposed to use for foods in its GRAS notification (GRAS No. 000137) (without the addition of sunflower oil) contains about 190 mg of cholesterol per 50 g.

Since it is highly unlikely that individuals would consume 50 g of dietary supplements containing EPA and DHA per day, FDA has decided that it is not necessary to consider, as a factor in the exercise of its enforcement discretion, that EPA- and DHA-containing dietary supplements weighing equal to or less than 5 g per RACC contain no more than 20 mg of cholesterol on a 50 g basis. However, FDA has decided that it is necessary to consider, as a factor in the exercise of its enforcement discretion, that EPA- and DHA-containing dietary supplements that weigh more than 5 g per RACC contain no more than 20 mg of cholesterol on a 50 g basis.

"Extra Lean" criterion for fish

FDA has defined fish in 21 CFR 123.3(d) as "fresh or saltwater finfish, crustaceans, other forms of aquatic animal life (including, but not limited to, alligator, frog, aquatic turtle, jellyfish, sea cucumber, and sea urchin and the roe of such animals) other than birds or mammals, and all mollusks, where such animal life is intended for human consumption." For the purpose of omega-3 fatty acid qualified health claims about fish, FDA intends to consider certain factors in the exercise of its enforcement discretion for use of these claims on "products that are essentially all fish." This category includes fish without any added ingredients and fish with a small amount of added fat or carbohydrate that meets the definition of an insignificant amount in 21 CFR 101.9(f)(1). Examples of "products that are essentially all fish" are raw fish, boiled fish, and broiled fish.

In the past, fish was given an exception for the "low saturated fat" criterion and "the low cholesterol" criterion, along with game meat, in the health claim about diets low in saturated fat and cholesterol and reduced risk of CHD (21 CFR 101.75 (c)(2)(ii)). Instead of the "low saturated fat and low cholesterol" criteria, fish was required to meet the "extra lean" criterion as defined in 21 CFR 101.62(e)(3) (i.e, contains less than 5 g total fat, less than 2 g saturated fat, and less than 95 mg cholesterol per reference amount customarily consumed and per 100 g.).

In applying the "extra lean" criterion to fish, FDA was not thinking about oily fish that are rich in EPA and DHA omega-3 fatty acids. Most fish that are a rich source of EPA and DHA exceed the "extra lean" criterion for saturated fat (2 g of saturated fat per RACC) but do not exceed the saturated fat disqualifying level (4 g of saturated fat per RACC). One of the ways that FDA determines whether to consider nutrient content eligibility criteria as a factor in the exercise of its enforcement discretion is whether there are risk reduction data among healthy individuals that would suggest that there may be a benefit from consumption of the food, even though the food does not meet the nutrient content eligibility criteria. Such data, for purposes of this review, would include an association with a lower risk of CHD, shown in observational studies conducted in apparently healthy individuals. Because the following observational studies: Albert et al., 1998, 2002; Hu et al., 2002; Mozaffarian et al., 2003 showed an association of fish intake with reduced risk of CHD in apparently healthy individuals, FDA has decided that the agency does not need to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for saturated fat. However, FDA has decided to consider, as a factor in the exercise of its enforcement discretion for products that are essentially all fish, that such products meet the "extra lean" criterion for cholesterol (95 mg of cholesterol per RACC). Most fish that are rich sources of EPA and DHA do not exceed the "extra lean" criterion for cholesterol; thus, this approach should not disqualify many products that are essentially all fish. As discussed earlier, FDA now considers the "low fat" criterion not important here; therefore, FDA is not considering the "extra lean" criterion for total fat, as a factor in exercising its enforcement discretion, which is not very different from how the agency approached its consideration of the "low fat" criteria as a factor for products that are essentially all fish.

B. Disqualifying Nutrient Levels

Under the general requirements for health claims (21 CFR 101.14(e)(3)) a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium established in § 101.14(a)(4). Section 101.14 applies to all health claims regardless of types of diseases and health-related conditions. The disqualifying nutrient levels vary for individual foods, meal products, and main dishes. Disqualifying total fat levels are above 13.0 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 26.0 g per label serving size for meal products, and above 19.5 g per label serving size for main dish products. Disqualifying saturated fat levels are above 4.0 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 8.0 g per label serving size for meal products, and above 6.0 g per label serving size for main dish products. Disqualifying cholesterol levels are

above 60 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 120 mg per label serving size for meal products, and above 90 mg per label serving size for main dish products. Disqualifying sodium levels are 480 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods, above 960 mg per label serving size for meal products, and above 720 mg per label serving size for main dish products.

The general requirements for health claims also provide for FDA to authorize a health claim for food despite the fact that a nutrient in the food exceeds the disqualifying level, if the agency finds that such a claim will assist consumers in maintaining healthy dietary practices. In such cases, the label must also bear a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level (21 CFR 101.14(e)(3)).